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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HABTE, KAHSAY	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 04/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/065,994	WEITHMANN ET AL.	
	Examiner	Art Unit	
	Kahsay Habte, Ph. D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-23* is/are rejected.

7)☒ Claim(s) *1 and 4-10* is/are objected to.

8)☐ Claim(s) _ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/23/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-23 are pending.

Election/Restriction

2. Applicant's election with traverse of Group I, Claims 1-23 in Paper filed 04/08/2004 is acknowledged. The traversal is on the ground(s) that the groups of inventions are Markush-type and thus, the requirement is improper under the PTO own guidelines regarding Markush-type of claims (MPEP 803.02). The examiner disagrees with applicants. Because different inventions share a common utility (inhibiting collagen synthesis) does not mean the inventions are related. For example, US Pat. No. 6,683, 069 (Fischer et al.) has the same utility as applicants, but one skilled in the art would not consider the non-heterocyclic compounds in Fisher '069 to be equivalent to the heterocyclic compounds (pyridines and pyrimidines) of the instant application. According to MPEP 803.02: "If the members of the Markush groups are sufficiently few in number or so closely related that a search and examination of the entire claims can be made without serious burden..." This does not apply to the instant, since Group I and Group II are not related. One skilled in the art would not consider a pyrimidine compound (diazine) as related to pyridine (monoazine). Furthermore coexamination of the additional group would require search of subclasses unnecessary for the examination of the elected claims. The search for the invention of Group II would include search of subclass 546/323. Therefore, coexamination of this additional invention would require a serious additional burden of search.

The requirement is still deemed proper and is therefore made FINAL.

3. The claims are drawn to multiple inventions for reasons set forth in the restriction requirement. The claims are examined only to the extent that they read on the elected invention. Cancellation of the non-elected subject matter is recommended in response to this Office Action.

Claim Objections

4. Claims 1-23 are objected because the numbering system is uses a letter with the number (i.e. [c1] - [c-25]). It is recommended that applicants delete the letter "c" from the numbering system.

5. Claims 13-17 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claims must be dependent in the alternate form. For example, claim 13 cannot multiply dependent on claim 12 and claim 3. See MPEP § 608.01(n).

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for therapy of certain diseases, does not reasonably provide enablement for prophylaxis of diseases "whose course involves an increased activity of matrix metalloproteinase 13". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There has been recited "prophylaxis" of disease whose course involves an increased activity of matrix metalloproteinase 13, but the specification is not enabled. To this day, the only way available is the treatment of diseases such as joint diseases, but it is not possible to prevent someone from having said diseases at first place. In a recent review article {Leeman et al. *Critical Review in Biochemistry and Molecular Biology*, 37(3):149-166(2002)} there is no mention of any prophylaxis of diseases whose course involves an increased activity of matrix metalloproteinase.

7. Claims 11 and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the therapy of breast cancer, does not reasonably provide enablement for the therapy of cancer diseases in general. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claim sets forth the therapy of cancer diseases generally. However, there never has been a compound capable of treating therapeutically cancer generally. There are compounds that therapeutically treat a range of cancers, but no one has ever been able

to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task.

The examiner invites applicants attention to page 161 of the review article by Leeman et al. that indicates "[t]he mechanism underlying the dysregulation of MMP-13 in cancer have still to be fully characterized. It is also becoming apparent that the MMPs have broad biological roles of which the best characterized is extracellular matrix degradation, but other roles in cell growth and regulation are now being identified, and further elucidation of the biological roles of MMP-13 can be expected." This clearly shows that the many of the biological roles of MMP-13 are the early stage of the study and characterization is needed especially for the dysregulation of MMP-13 in cancer cells. Note that Figure 3 (page 156) shows that MMP-13 has a complex role in the overall activation cascade interacting with other 5 MMPs. MMP has a wide range of

substrates. Note that there is no mention in the review article of any use of MMPs for therapeutic purposes. This indicates that the study of MMPs is at its early stage and that further studies are needed to explore the use of MMPs for therapeutic purposes.

When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs Novo Nordisk*, 42 USPQ2nd 1001, 1006.

8. Claims 11 and 21-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There has been recited a method for prophylaxis and therapy of chronic diseases of locomotor system, but the specification is not enabled for such a scope.

Locomotor system deals with components of the structure/function relationships of bone, muscle and joints, the pathologic processes affecting these and the processes of repair and healing. The skeleton and skeletal muscles work together to allow movement. The brain controls the movements of the body, using information from:

- The eyes.

- The ears, including special canals, which give us a three-dimensional sense of motion.
- The muscles themselves, called 'muscle sense' or kinaesthesia.

The skeleton

The skeleton is made up of 206 bones. Bones are a form of connective tissue reinforced with calcium and bone cells. Bones have a softer centre, called marrow, where blood cells are made. The three main functions of the skeleton are:

- **Support** - the body is supported and shaped by the skeleton; for example, upright posture would be impossible without a spine.
- **Protection** - our internal organs are protected by our skeleton, such as the brain inside the skull, the heart and lungs inside the ribcage.
- **Movement** - most skeletal muscles are attached to bones in opposite working groups, like the bicep and tricep muscles of the upper arm.

Muscle fibres

Skeletal muscles operate under voluntary control. An example of involuntary muscles are those that line the digestive system. Skeletal muscles are made up of muscle fibres, bundled together. Each fibre can contract or relax on demand. All fibres contract together to shorten a muscle. The command to contract or relax is given by the brain

and relayed to the muscle by nerves.

Working in pairs

Generally, muscles move the skeleton by working in opposite pairs. For instance, if you bend your elbow, your biceps (muscles on the front of the upper arm) contract and the triceps (muscles on the back of the upper arm) relax. It works the other way if you straighten your arm - the triceps contract while the biceps relax. In some joints, like the shoulder joint, many different muscles are attached. This allows even greater freedom of movement.

Common problems

Some of the more common problems of the locomotor system include:

- **Arthritis** - problems within the joints, such as inflammation
- **Broken bones** - caused by falls or accidents
- **Slipped disc** - when cartilage in the spinal column shifts out of position.

In addition, bone disease, CNS disorders, personal injuries to the brain or spinal cord, etc. are some of the conditions that can cause chronic diseases of locomotor system.

Note that the movement of any parts of a body involves a signal from a central nervous system. Thus, the claim also covers any CNS disorders that affect the movement of a body. For example, Parkinson's disease is a central nervous system disorder, but it is covered under "diseases of locomotor system." Since diseases of

locomotor system would cover problems in any of the above parts of the body arise from different origins, and differ significantly one from the other, an enablement rejection is proper.

Note that in the review article by Leeman et al. there is no mention of any method for prophylaxis or therapy of disease for locomotor system whose course involves an increased activity of matrix metalloproteinase.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-3 and 11-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention:

a. In claims 2 and 11-12 the phrase "related chemical entity" is indefinite. What related chemical entity? Related how? What is covered and what is not?

b. In claim 3, the term "expect" is not clear. Does applicants mean except?

c. Regarding claims 18, 20, 22 and 23, the phrases "include" or "including" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

d. In claims 11-12, there has been recited "disease whose course involves an increased activity of matrix metalloproteinase 13". The scope of claims 11-12 is unknown. Which diseases are these? Determining whether a given disease responds or does not respond to such mediator will surely involve undue experimentation. Suppose that a given inhibitor X when administered to a patient with Disease D does not obtain a response. Does one then conclude that Disease D does not fall within this claim? Keep in mind that:

A. It may be that the next patient will respond. It is quite common for pharmaceuticals to work only with some people, not all. Thus, how many need to be tested?

B. It may be that the wrong dosage or dosage regimen was employed. It is quite common for pharmaceuticals to work at one dosage, but not at another which is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? Thus, how many dosages and dosage regimens must be tried before one is certain that this pharmaceutical won't affect Disease D?

C. It may be that X simply isn't potent enough for Disease D, but that another inhibitor Y is potent enough, so that D really does fall within the claim. Thus, how many different mediators must be tried before one concludes that D doesn't fall within the claim?

D. Conversely, if D responds to Y but not to X, can one really conclude that D falls within the claim? It may be that the X result is giving the accurate answer, and that the success of Y arises from some other unknown property which Y is capable of. Thus, when mixed results are obtained, how many more pharmaceuticals need be tested?

E. Finally, suppose that X really will work, but only when combined with Z. There are for example, agents in the antiviral and anticancer technology which are not themselves effective, but the disease will respond when the agents are combined with something else.

As a result, determining the true scope of the claim will involve extensive and potentially open-ended research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

e. In claims 11-12, the phrase "whose course involves an increased activity of matrix metalloproteinase 13" is indefinite. What are those diseases? Note that the phrase covers the diseases caused by increased activity of matrix metalloproteinase 13 and also covers the disease that are effected by increased activity of matrix metalloproteinase 13. What is applicant's intention? Note that there is no well-defined list of disease of MMP-13 caused disease which are treated with MMP-13 antagonists.

f. In claim 21, the phrase "chronic diseases of locomotor system" is not clear. What are covered and what are not? How can one tell if a disease is a chronic disease of locomotor system or not? Note that this is not a well-defined category.

Conclusion

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte, Ph. D. whose telephone number is (571) 272-0667. The examiner can normally be reached on M-F (9.00AM- 5:30PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on (571) 272-0674. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Kahsay Habte, Ph. D.
Examiner
Art Unit 1624

Mark L. Berch
Primary Examiner
Art Unit 1624

KH
April 21, 2004